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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,423	10/16/2001	Avi J. Ashkenazi	GNE.2630P1C21	5291

7590 01/10/2005

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EXAMINER	
LE, EMILY M	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,423	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 58-62 are pending and under examination.

Priority

2. As noted in the previous office action, Applicant is accorded the effective filing date of 10/16/2001 because the protein in which the claimed antibody binds lacks a utility.

Applicant maintains that the claimed invention is entitled to the priority date of 04/01/1998, because the provisional filed then discloses that the PRO701 polypeptide possess the biological activity related to that of the neuroligin family and that neuroligins constitute a multigene family of brain specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Additionally, Applicant asserts that the claimed invention have utility because neurexins and neuroligins have also been reported in the art, after the filing date of the claimed invention, as adhesion molecules in a Ca2+ dependent reaction that is regulated by alternative splicing of beta neurexins. Applicant also asserts that the protein to which the claimed antibody binds is a novel neuroligin functioning protein that mediates recognition processes between neurons, while pointing to the teaching of Bollinger et al. and Jamain et al. for support. Bollinger et al. teaches of neuroligin 4, which is similar to the protein to which the claimed antibody binds, binds to PSD-95. Jamain et al. teaches that mutations of neuroligin 4 are associated with autism.

Applicant's above submission has been considered, however, it is not found persuasive. The claimed invention must have a credible, specific and substantial, or well-established utility at the time of filing. Applicant's submission regarding the recent discovery that neurexins and neuroligins are adhesion molecules in a Ca2+ dependent reaction that is regulated by alternative splicing of beta neurexins, proteins that are similar to those that the claimed antibody binds can bind to PSD-95, and mutations in the protein that is similar to those that the claimed antibody binds are associated with autism cannot be used to provide a utility for the claimed invention and the protein to which it binds. The use of discoveries that are established after the filing date to instate a utility to the claimed invention is not in accordance with USPTO practice and procedure.

Additionally, while it has been noted that Applicant discloses that the protein to which the claimed invention binds have homology (unspecified percentage) to neuroligins; however, mere identification that a protein belongs to a family of proteins, while indicative of evolutionary relatedness, is not indicative of function, nor by extension, of utility. In paragraph 1453, the specification states that the protein to which the claimed invention binds "may be employed both in vivo for therapeutic purposes and in vitro". However, this statement is conjecture and non-specific as to what kind of therapeutic purposes. There is no evidence to indicate that the protein in which the claimed invention binds would have biological activity as that of proteins that belongs to the neuroligin family. Furthermore, such statement is merely an invitation to experiment to determine a utility for the protein. Additionally, there is no biological activity,

expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed, at the time of filing, as being associated with PRO701. Without any information as to the specific properties of the protein to which the claimed invention binds, the mere identification of such as having homology to a neuroligin is not sufficient to impart any particular utility to the claimed antibodies.

Claim Rejections - 35 USC § 101

3. Claims 58-62 remains rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicant submits that neuronal survival assay is a well recognized and well used assay for measuring the growth of neural cells, while pointing to Memberg et al. and Lewis et al. for support.

Applicant's above submission has been considered, however, is not found persuasive. The Examiner is aware of the teaching of the MPEP § 2107(B)(1). A claimed invention has utility when it meets the three prong tests or the claimed invention has a well-established utility. The three prongs that are used to determine utility are 1) credible, 2) specific, and 3) substantial. In the instant, the assay that is applied fails to provide a credible utility for the protein in which the claimed invention binds. In the instant, the Examiner is not questioning the practicality and the validity of the assay as it is used in the art. However, in the instant, the assay fails to render any evidence that would signify that the protein to which the claimed antibody binds would be useful in treating neuroblastomas, gliomas, glioblastomas and the like. Furthermore, a search of

the literature fails to reveal correlation between the instant assay and the alleged therapeutic uses, as exemplified by Memberg et al. and Lewis et al. Thus, the assay fails to provide a credible utility for the claimed invention.

Applicant also submits a declaration by Sherman Fong, Ph.D. to show that there are specific immune inhibitory utilities for compounds identified by an MLR assay. Dr. Fong, in the declaration submits that immuno-inhibitory molecules are important and are very desirable in the treatment of cancer and the effectiveness of previously identified treatments of cancer. Applicant also points Steinman et al. and Peterson et al. for support.

Applicant's above submission has been considered, however, it is not found persuasive. Applicant's submission is not specific to the claimed invention. The Examiner is not questioning the status of the assay as it is used in the art. In the instant, the assay fails to provide a substantial and specific utility for the protein in which the claimed invention binds. In the instant, Applicant uses the assay to determine if the protein to which the claimed invention binds inhibits the proliferation of stimulated T-lymphocytes. Applicant asserts that proteins that tested positive in the assay would be useful therapeutically where suppression of an immune response is beneficial. Such asserted utility is not specific since any compounds that failed or tested positive in this assay can be deemed as therapeutic. Applicant has not disclosed of a substantial and specific immune inhibitory utility for the compounds identified by the MLR assay.

As noted, the ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or

for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial (page 354, line 10-11) is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any.

Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T

cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-209, 246-247 of "Basic and Clinical Immunology," 1994. See also, "Manual of Clinical Laboratory Immunology," 6th Edition at pages 1164-1166.

Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

Additionally, difficulties arise in quantification when using MLC as a test for T cell

function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibility in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. When running the MLC assay for determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunology"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogenic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell.

The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary—which Applicant failed to submit instantly.

Applicant further submits that the protein to which the claimed invention binds have utility because the protein to which the claimed invention binds possess the

biological activity related to that of the neuroligins family. Applicant submits that neuroligins constitute a multigene family of brain specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Additionally, Applicant asserts that the claimed invention have utility because neurexins and neuroligins have also been reported in the art, after the filing date of the claimed invention, as adhesion molecules in a Ca2+ dependent reaction that is regulated by alternative splicing of beta neurexins. Applicant also asserts that the protein to which the claimed antibody binds is a novel neuroligin functioning protein that mediates recognition processes between neurons, while pointing to the teaching of Bollinger et al. and Jamain et al. for support. Bollinger et al. teaches of neuroligin 4, which is similar to the protein to which the claimed antibody binds, binds to PSD-95. Jamain et al. teaches that mutations of neuroligin 4 are associated with autism.

The above submission has been considered, however, is not found persuasive. The claimed invention must have a credible, specific and substantial, or well-established utility at the time of filing. Applicant's submission regarding the recent discovery that neurexins and neuroligins are adhesion molecules in a Ca2+ dependent reaction that is regulated by alternative splicing of beta neurexins, proteins that are similar to those that the claimed antibody binds can bind to PSD-95, and mutations in the protein that is similar to those that the claimed antibody binds are associated with autism cannot be used to provide a utility for the claimed invention and the protein to which it binds. The use of discoveries that are established after the filing date to instate a utility to the claimed invention is not in accordance with USPTO practice and procedure.

Additionally, while it has been noted that Applicant discloses that the protein to which the claimed invention binds have homology (unspecified percentage) to neuroligins; however, mere identification that a protein belongs to a family of proteins, while indicative of evolutionary relatedness, is not indicative of function, nor by extension, of utility. In paragraph 1453, the specification states that the protein to which the claimed invention binds "may be employed both in vivo for therapeutic purposes and in vitro". However, this statement is conjecture and non-specific as to what kind of therapeutic purposes. There is no evidence to indicate that the protein in which the claimed invention binds would have biological activity as that of proteins that belongs to the neuroligin family. Furthermore, such statement is merely an invitation to experiment to determine a utility for the protein. Additionally, there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed, at the time of filing, as being associated with PRO701. Without any information as to the specific properties of the protein to which the claimed invention binds, the mere identification of such as having homology to a neuroligin is not sufficient to impart any particular utility to the claimed antibodies.

In view of the discussion above, the claims remain rejected under 35 U.S.C. 101.

4. Claims 58-62 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

5. The rejection of claims 58-62 under 35 U.S.C. 102(b) as being anticipated by Ichtchenko et al, ("Neuroligin 1: A Splice Site-Specific Ligand for β–Neurexins", 1995) is maintained.

Applicant submits that the art recognized meaning of "specific binding" is that the antibody that specifically binds to a particular antigen dos not significantly cross-react with another antigen. Therefore, the claimed invention clearly refers to an antibody that is able to bind to the protein without significantly cross reacting with another antigen. Applicant is not required to identify the unique epitope in the protein to which the claimed invention binds.

Applicant's submission has been considered, however, it is not found persuasive. Applicant is correct to note that Applicant is not required to identify the unique epitope in the protein which the claimed invention binds, however, in the absence of evidence that proves that the claimed antibody is different from that of the antibody that Ichtchenko et al. teaches, the rejection stands. In the instant, Ichtchenko et al. teaches of antibody that binds to a neuroligin protein. Applicant discloses that the protein to which the claimed invention binds have homology to neuroligins proteins. Thus, in view of the teaching that is shared between the two proteins, the antibody of Ichtchenko et al. would necessarily bind to the same protein in which the claimed invention binds.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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